Sub D2

31. (Amended) [A] The method [according to] of claim 29 wherein the analogue of NRH is able to permeate the target cell membrane.

B3

32. (Amended) [A] The method [according to] of claim 29 wherein the target cell is a tumour.

33. (Amended) [A] The method [according to] of claim 29 the method further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

B4

41. (New) The method of claim 29, wherein the analogue of NRH is 1-(carboxamidomethyl)-dihydronicotinamide.

Add D3

Remarks

Claims 1-40 are pending. Claims 29, and 31-33 have been amended. Claims 1-28, 30 and 34-39 have been canceled. Claims 1-28 and 34-39 have been withdrawn from consideration as being drawn to a non-elected invention. Per the examiner's suggestion, claim 29 was amended to define the pro-drug of claim 29 as CB 1954. Support for claim 29 can be found, for example, on page 39, line 8. Claims 31-33 were amended to more clearly define what applicants consider to be their invention. Support for new claim 41 can be found, for example, on page 61, lines 1-20. A copy of all of the pending claims as they are believed to have been amended is attached to this Amendment as an appendix.

The present invention is directed to treating human cancer via the administration of the pro-drug CB 1954 which is converted to a cytotoxic drug by the action of human NQO2 and NRH or an analogue thereof. The cells to be targeted express NQO2.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 29-33 and 40 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The examiner asserts that the specification is lacking correlation between *in vitro* data/results and clinical work. The applicants agree that the *in vivo* environment is complex and that it can be difficult to extrapolate from *in vitro* results to human therapeutic efficacy. However, the examiner should not disregard that the present invention incorporates human NQO2 which was identified on the basis of it's homology to DT-diaphorase (NQO1) (page 7, lines 27-28) and has been shown to potentiate the effects of NRH on CB 1954 cytotoxicity towards human cells (page 8, lines 18-21). CB 1954 is a *proven* anti-tumor agent as defined by *in vivo* work in rats, in which CB 1954 is activated by the enzyme NQO1 (please see page 5, line 26 to page 7, line 16). It has *also* been shown that human NQO2 can activate CB 1954 in the presence of a specific co-substrate (which can be administered to animals). The cytotoxic *product* of this activation reaction is *identical* to that produced by rat NQO1. It is therefore not unreasonable to predict that a similar cytotoxic effect would occur in humans. The actual compound responsible for the cytotoxic effect *is the same* as that shown to elicit the same effect

in response to activation by NQO1 and therefore will function as claimed. There should not be a requirement to extrapolate from *in vitro* data for a *new* cytotoxic compound.

The applicants partially agree that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon. However, careful extrapolations have been made based on results from these types of systems for years. As stated above, the applicants have not extrapolated the efficacy of the resultant cytotoxic compound from *in vitro* studies. The applicants have used the examples as a way to illustrate that the administration of co-substrates to living cells is achievable and their desired effects on the reactions *to produce* a cytotoxic compound, obtainable. The co-substrate is only required to permeate the cell membrane. The specification is replete with successful examples of permeation by co-substrates (see Figure 9, for example). Figures 11 and 12 are drawn to the effects of the co-substrates on the reactions that catalyze the formation of the cytotoxic compound from the prodrug.

Rejection Under 35 U.S.C. § 112, second paragraph

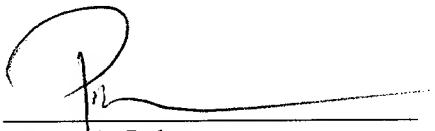
Claims 29-33 and 40 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 29-33 and 40 were rejected as being vague and indefinite for reciting "substantially" in base claim 29. The applicants have deleted the term "substantially" from base claim 29. Per the examiner's suggestion, claims 29-30 have been amended to recited "wherein

the prodrug is CB 1954". The applicants respectfully submit that the foregoing amendments relieve the present application of all rejections under 35 U.S.C. § 112, second paragraph.

Allowance of claims 29-33 and 40 is respectfully solicited.

Respectfully submitted,



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Date: July 10, 2001

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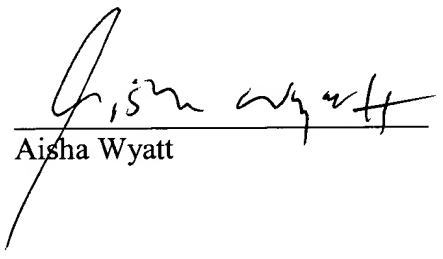

Aisha Wyatt

Date: July 10, 2001

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

29. (Amended) A method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to the patient a prodrug which is converted to a [substantially] cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2, wherein the prodrug is CB 1954.

31. (Amended) [A] The method [according to] of claim 29 wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) [A] The method [according to] of claim 29 wherein the target cell is a tumour.

33. (Amended) [A] The method [according to] of claim 29 the method further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

40. The method of claim 29 wherein the patient has cancer.

41. (New) The method of claim 29, wherein the analogue of NRH is 1-(carboxamidomethyl)-dihydronicotinamide.

Clean Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

29. (Amended) A method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to the patient a prodrug which is converted to a cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2, wherein the prodrug is CB 1954.

31. (Amended) The method of claim 29 wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) The method of claim 29 wherein the target cell is a tumour.

33. (Amended) The method of claim 29 the method further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

40. The method of claim 29 wherein the patient has cancer.

41. (New) The method of claim 29, wherein the analogue of NRH is 1-(carboxamidomethyl)-dihydronicotinamide.

Marked Up Version of Amended Specification Paragraphs

Pursuant to 37 C.F.R. § 1.121(b)(1)(iii)

[Figure 10 shows the plasmids pIRES-P and H6] Figures 10A and 10B show the plasmids pIRES-P and H6, respectively.

ATL1 #469362 v1